

thereof, but only for the treatment of non-small cell type lung tumors and only with the co-administration of paclitaxel. (In this regard, it is noted for the Examiner's benefit that the working example on page 7, lines 8-12 illustrates a standard chemotherapy regimen of paclitaxel and carboplatin, not paclitaxel alone.)

To expedite matters, the present amendment limits the cytokine inducer to [R-(R\*,R\*)]-N-[(R)-6-carboxy-N<sup>2</sup>-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]-L-lysyl]-alanine or a pharmaceutically acceptable salt thereof. With respect to the enablement of using this compound in combination with other chemotherapeutic agents besides paclitaxel and carboplatin to treat other solid tumors in addition to the non-small cell lung tumors, Applicants respectfully believe that the rejection is not justified for the following reasons.

It is clear that the written disclosure provides enablement to the practitioner of ordinary skill in the oncology field to be able to practice the scope of the present invention without undue experimentation. The specification adequately explains the invention and demonstrates how to practice the claimed method with two working examples in the form of an *in vivo* standard pharmacological test procedure and a successful clinical trial. There is no reason why the practitioner would question the results or the accuracy of the statements with respect to the method of treating solid tumors with [R-(R\*, R\*)]-N-[(R)-6-carboxy-N<sup>2</sup>-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]-L-lysyl]-alanine or a pharmaceutically acceptable salt thereof and a chemotherapeutic agent. The practitioner would reasonably expect that the same or substantially similar results shown in the application could be obtained in the context of cancers beyond non-small cell lung tumors and the use of alternative chemotherapeutic agents besides paclitaxel and carboplatin.

Instead of a blanket presumption of unknown predictability in the chemical or biological arts, the predictability factor refers more to the ability of the ordinary chemist or biologist to extrapolate the disclosed results to the claimed invention. It does not require a disclosure of every operable species or exemplification of each and every embodiment. The predictability factor only determines if the ordinary practitioner would have reasonable doubt as to the accuracy of treating solid tumors with a chemotherapeutic agent and [R-(R\*,R\*)]-N-[(R)-6-carboxy-N<sup>2</sup>-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]-L-lysyl]-alanine as taught by the present specification.

The Examiner, however, has not given any scientific principle or literature reference to prove any reasonable doubt in the oncology field. Rather, he should take into consideration that certain chemotherapeutic agents and combinations thereof, which are known to be useful in the treatment of solid tumors but have poor response and survivor rates in the more advanced stages of cancers, would benefit from the cytokine inducer of the present invention. Furthermore, one of ordinary skill in the art would know which regimen of the well-defined group of chemotherapeutic agents to select to treat each particular solid tumor for purposes of the claimed method.

For example, standard treatment options for metastatic breast cancer and melanomas include vinca alkaloids (*e.g.*, vincristine, vinblastine, vinorelbine), platinum compounds (*e.g.*, cisplatin, carboplatin) and taxanes (*e.g.*, paclitaxel) while standard treatment options for endometrial cancers include taxanes (*e.g.*, paclitaxel) with doxorubicin or platinum compounds like cisplatin with doxorubicin (see the attached true copies of online information available from the National Cancer Institute in illustration of this point as Exhibits A-C). In addition to non-small cell lung tumors and the foregoing cancers, paclitaxel is used to treat soft tissue sarcomas, head and neck cancer, small cell lung cancer and bladder cancer, to name a few. Similarly, doxorubicin, carboplatin, cisplatin, vincristine and the like have a broad spectrum of activity against a variety of solid tumors (see the attached true copies of online information available from NIH MedlinePlus as Exhibits D-H). These chemotherapeutic agents have one main biological property in common: They slow or stop the growth of cancer cells in the body. In other words, the cytotoxic agents target the cancer cells.

On the other hand, looking at what the specification actually teaches to the ordinary practitioner, Applicants demonstrate that the formula I compound is totally devoid of anticancer activity. The compounds do not inhibit tumor cell growth in nude mice or in tissue culture (see page 7, lines 1-6, of the application). Yet, surprisingly, when the cytokine inducer compounds are combined with a chemotherapeutic agent, they demonstrate enhanced activity against H-157 (see the excellent results in Table 1 on page 6 of the application).

The important fact that the H-157 line grows in nude mice is highly suggestive that the tumor cell line is representative of other growing solid human tumors in that not every tumor line will grow in nude mice. Also, the combination therapy in the working examples is not

directed at the tumor itself, but rather, at the host response to the tumor, *i.e.*, the cytokine inducer works as a bioresponse modifier to enhance the anti-tumor activity of art-recognized chemotherapeutic agents. The evidence for this premise is found in the showing that the tumor cell growth in tissue culture is not inhibited by the representative drug of formula I.

The *in vivo* standard pharmacological test procedure and the successful clinical trial demonstrate that the cytokine inducer of the invention significantly improved the anti-tumor activity of two chemotherapeutic agents, paclitaxel and carboplatin, in the treatment of non-small cell lung tumors. It would be a matter of routine experimentation to test alternative chemotherapeutic agents with [R-(R\*,R\*)]-N-[(R)-6-carboxy-N<sup>2</sup>-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]-L-lysyl]-alanine in different tumor cell lines as illustrated with the H-157 cell line. There is no reason for the artisan to believe that the cytokine inducer cannot effectively potentiate the treatment of other solid tumors by using the compound with other known chemotherapeutic agents that target cancer cells. In sum, the specification provides sufficient enablement to support the patentability of the claimed method.

In view of the proffered evidence, the foregoing comments and the prior arguments of record, it is respectfully requested that the Examiner withdraw the rejection of the pending claims under 35 U.S.C. § 112, first paragraph.

The Examiner rejects Claims 1 and 3 under 35 U.S.C. § 112, second paragraph, for reasons given on page 10 of the Office action. Since the claims are being limited to the exemplified cytokine inducer to expedite matters, the amendment renders this rejection moot.

In terms of the art rejection, the basis for the rejection is confusing. The Examiner kindly indicates that the rejection of Claims 1, 3 and 5-7 under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,545,662 in view of The Merck Index is withdrawn (see par. 15, page 13 of the Office action). Yet it is also stated that the rejection of Claims 1, 3 and 5-7 (now Claims 15-18) under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,545,662 in view of The Merck Index is maintained (see par. 13, page 11 of the Office action). Clarification of the record is respectfully requested.

Taking the present invention as a whole, the unique method of **treating solid tumors** using a combination of the cytokine inducer and a chemotherapeutic regimen has not been taught or suggested in the '662 patent. Rather, the patent only teaches the ordinary practitioner

that the cytokine inducer can be used to increase neutrophil counts as an adjuvant to chemotherapy or accelerate neutrophil recovery to combat the negative side effects of cancer chemotherapy. The instantly claimed method of treating solid tumors is a totally new concept and new utility for the cytokine inducer that was not previously described in the art.

Although the Examiner asserts that the '662 reference additionally qualifies as prior art under another subsection of 35 U.S.C. § 102 and is not disqualified as prior art under 35 U.S.C. § 103(c) (see par. 11, page 11 of the Office action), no clear-cut rejection of the claims under 35 U.S.C. § 102 as being anticipated by the '662 patent has been made in the record.

If the Examiner had intended to reject the claimed invention as being anticipated by the cited art, it seems to be based on his statement that the reference allegedly teaches in its abstract that compound no. 28 is useful "in the treatment of cancer." This reasoning, however, ignores the plain and simple fact that the compound does not have anti-tumor activity. This total absence of anti-tumor activity is a key factor in understanding what the patent, as a whole, teaches to the ordinary practitioner. Taking the lack of anti-tumor activity in consideration, it becomes clear that there is no true identity of invention. Patentees were not proposing that their compounds be used for treating cancer *per se*. The implication is not substantiated by the rest of the patent in that actual chemotherapeutic use as a cytotoxic agent is not exemplified, claimed or even possible in light of the inactivity against tumors. The claimed method of the present invention is simply not described or implied within the explicit teachings of the patent.

The '662 patent does not expressly teach or speculate that the compounds of formula I would be useful in the treatment of solid tumors since patentees could not effectively treat solid tumors with the formula I compounds alone. Applicants demonstrate that the claim-recited cytokine inducer compound of formula I is totally devoid of anticancer activity; it did not inhibit tumor cell growth in nude mice or in tissue culture (see page 7, lines 1-6, of the application). Since the compound of formula I lacks efficacy in treating cancer and anti-tumor activity is not an inherent property, the practitioner has absolutely no motivation to combine the compounds of the '662 patent with chemotherapeutic agents and expect success in treating solid tumors. Certainly, the '662 patent does not disclose or suggest a combination of a chemotherapeutic agent with [R-(R\*,R\*)]-N-[(R)-6-carboxy-N<sup>2</sup>-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]-L-lysyl]-alanine to treat solid tumors as described and

claimed herein. There is absolutely no evidence that the patent anticipates the present invention or renders it obvious.

In view of the foregoing remarks and the remarks of record, Applicants respectfully ask that the Examiner kindly withdraw the art rejection of Claims 15-18 and allow the application.

The undersigned attorney wishes to thank the Examiner for taking the time to discuss the scope of the claims with her and provide helpful advice in this case. It was greatly appreciated.

Accordingly, it is believed that this application is now in proper condition for an allowance and such favorable treatment is respectfully solicited.

Respectfully submitted,

WYETH

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